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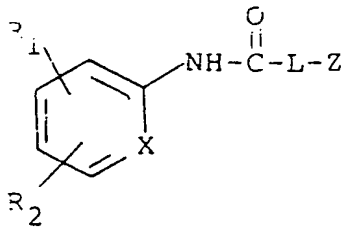
(54) Novel compounds.

(57) Compounds of formula (I), and pharmaceutically acceptable salts thereof:



(I

wherein

L is NH or O;

X is a moiety capable of hydrogen bonding to the NH group depicted in formula (I);

R_1 and R_2 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6}alkylsulphinyl, carboxy, C_{1-6} alkoxycarbonyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or

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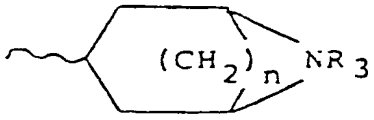
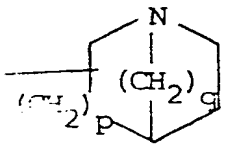
N-(aminosulphonyl)-C_{1-4}alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8}cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5}polymethylene; and

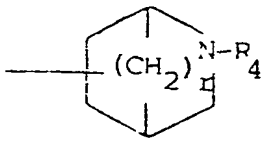
Z is a group of formula (a), (b) or (c)



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3: and

R_3 or R_4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8}cycloalkyl-C_{1-2}alkyl or C_{2-7} alkenyl-C_{1-4} alkyl; having 5-HT M-receptor antagonist activity, a process for their preparation and their use as pharmaceuticals.

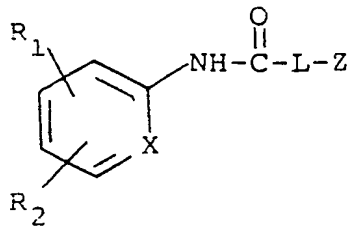
NOVEL COMPOUNDS

This invention relates to novel compounds having useful pharmacological properties, to pharmaceutical compositions containing them, to processes and intermediates for their preparation, and to their use as pharmaceuticals.

GB 2100259A and 2125398A and EP-A-158265 describe benzoates and benzamides having an azabicyclic side chain and possessing 5-HT antagonist activity.

A class of novel, structurally distinct compounds has now been discovered. These compounds have 5-HT M-receptor antagonist activity, anti-emetic activity and/or gastric motility enhancing activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

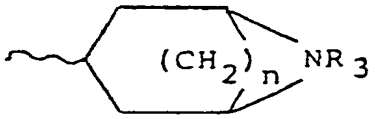
wherein

L is NH or O;

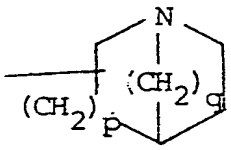
X is a moiety capable of hydrogen bonding to the NH group depicted in formula (I);

R_1 and R_2 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6}alkylsulphinyl, carboxy, C_{1-6} alkoxycarbonyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4}alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8}cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5}polymethylene; and

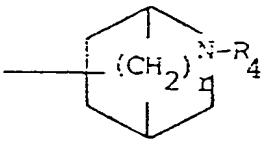
Z is a group of formula (a), (b) or (c)



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and
R_3 or R_4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8}cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl.

Preferably L is NH.

X is usually C-OR_5 wherein R_5 is hydrogen, C_{1-6} alkyl, C_{3-7} alkenyl-methyl, phenyl or phenyl C_{1-4} alkyl in which either phenyl moiety may be substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halo (such as fluoro, chloro or bromo) or X is a moiety C-R_6 wherein R_6 is CO_2R_7 wherein R_7 is hydrogen or C_{1-6} alkyl, $CONR_8R_9$ or $SO_2NR_8R_9$ wherein R_8 and R_9 are independently hydrogen or C_{1-6} alkyl or together are C_{4-6} polymethylene, NO_2, $(CH_2)_mOR_{10}$ wherein m is 1 or 2 and R_{10} is C_{1-6} alkyl or $S(O)_nR_{11}$ wherein n is 0, 1 or 2 and R_{11} is C_{1-6} alkyl. X may also be N^+-O^-.

Suitable examples of alkyl groups in R_5, R_7, R_8, R_9, R_{10} and R_{11} include methyl, ethyl, n and iso-propyl, n-, sec-, iso-and tert-butyl, preferably methyl.

Suitable values for R_5 when C_{3-7} alkenyl-methyl include prop-2-enyl, but-2-enyl, but-3-enyl, 1-methylenepropyl and 1-methylprop-2-yl in their E and Z forms where stereoisomerism exists.

Preferred examples of X include C-OCH_3, C-OC_2H_5, C-OC_3H_7, C-CO_2CH_3, C-$CO_2C_2H_5$ and $SO_2N(CH_3)_2$

Values for R_1 and/or R_2 include hydrogen, fluoro, chloro, bromo, CF_3, methyl, ethyl, methoxy, ethoxy, methylthio, ethylthio, acetyl, propionyl, acetylamino, methylsulphonylamino, methylsulphinyl, carboxy, methoxycarbonyl, hydroxy, nitro; and amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-methylamino any of which may be optionally substituted by one or two methyl groups or by a cyclopentyl or cyclohexyl group or disubstituted by C_4 or C_5 polymethylene; R_1 is often hydrogen and R_2 is hydrogen or a 4-substituent, such as halo or methoxy. R_1 and R_2 are preferably both hydrogen.

Preferably n is 2 or 3 and p, q and r are 1 or 2.

Examples of R_3/R_4 when C_{1-7} alkyl include as groups of interest C_{1-3} alkyl such as methyl, ethyl and n- and iso-propyl. Within C_{1-7} alkyl, C_{4-7} alkyl are also of interest, especially those of the formula $(CH_2)_uR_9$ wherein u is 1 or 2 and R_9 is a secondary or tertiary C_{3-6} alkyl group. Examples of C_{4-7} alkyl include n-, sec - and tert-butyl, n-pentyl, n -heptyl, and iso-butyl, 3-methylbutyl, and tert -butylmethyl.

Examples of R_3/R_4 when C_{3-8} cycloalkyl-C_{1-2} alkyl include in particular those wherein the cycloalkyl moiety is cyclohexyl or cyclopropyl. Examples of include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, tert-butylmethyl, iso-propylmethyl, iso-propylethyl and tert-butylethyl.

R_3/R_4 may in particular be cyclopropylmethyl, cyclohexylmethyl, iso-propylmethyl, tert-butylmethyl or iso-propylethyl, preferably tert-butylmethyl.

Examples of R_3/R_4 when C_{2-7} alkenyl-C_{1-4} alkyl include prop-2-enyl, but-2-enyl, but-3-enyl and 1-methyl-prop-2-enyl in their E and Z forms when stereoisomerism exists.

R_3/R_4 is preferably methyl or ethyl, most preferably methyl.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventonal acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, lactic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-l-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_{10}-T wherein R_{10} is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7}cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_{10} include methyl, ethyl and n-and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

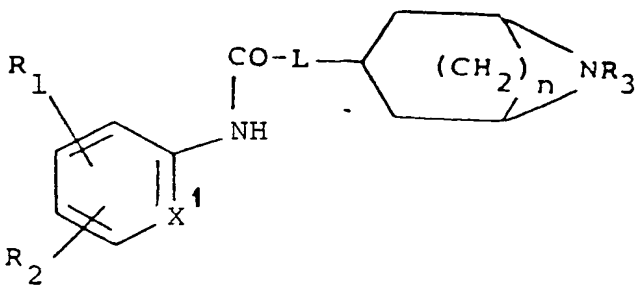
The compounds of formula (I) may also form internal salts such as pharmaceutically acceptable N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

It will also be realised that compounds of formula (I) may adopt an endo or exo configuration with respect to L. The endo configuration is preferred.

A group of compounds within formula (I) is of formula (II):

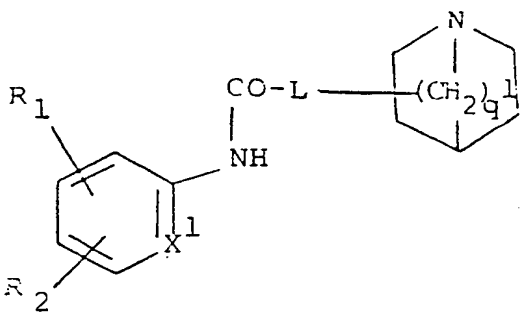


(II)

wherein X' is COR_5 or a group C-R_6 as hereinbefore defined; and the remaining variables are as defined in formula (I).

Examples of the variables and preferred variables are as so described for corresponding variables in relation to formula (I).

A further group of compounds within formula (I) is of formula (III):

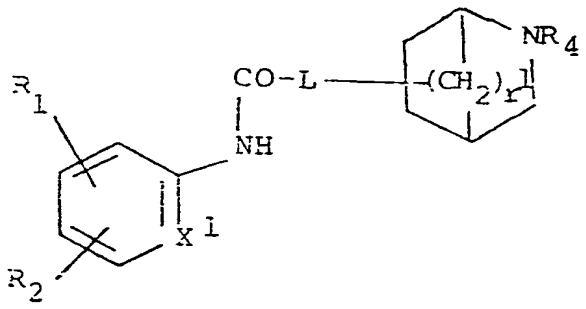


(III)

wherein q' is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are as so described for the corresponding variables in formula (I).

There is a further group of compounds within formula (I) of formula (IV):

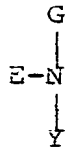


(IV)

wherein r^1 is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are so described as the corresponding variables in formula (I).

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (V):

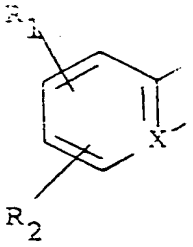


(V)

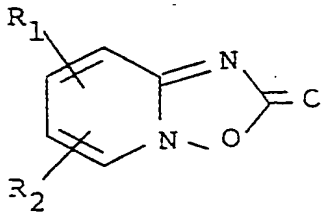
with a compound of formula (VI):

$J\text{-}Z^1$ (VI)

wherein E is:



wherein X' is X as defined, or N, and Y is hydrogen or joined to G as defined, or (when X is $N^+\text{-}O^-$) E and Y together are joined to G to form (V)'



G is COQ_1 where Q_1 is a group displaceable by a nucleophile, G and Y together =C=O or G is joined to E as defined, or G is hydrogen (when Y is hydrogen); and, when G is COQ_1 or G-N-Y is N=C=O, J is NH_2, or OH or a reactive derivative thereof or, when G is hydrogen, J is a group containing an activated carbonyl group capable of forming a CO-L-linkage wth the compound of formula (V); Z^1 is Z as defined or Z wherein R_3/R_4 is replaced by a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting any R_1 and R_2 group to another R_1 and R_2 group respectively, converting Z^1, when other than Z, to Z; converting X' when N to N^+-O^- or X to other X; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of leaving groups Q_1, displaceable by a nucleophile, include halogen such as chloro and bromo, C_{1-4} alkoxy, such as CH_3O and C_2H_5O-, PhO-or activated hydrocarbyloxy, such as Cl_5C_6O-or Cl_3CO-.

If a group Q_1 is a halide, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran - (THF) or dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0°-100°C, in particular 10-80°C are suitable.

If a group Q_1 is C_{1-4} alkoxy, phenoxy or activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as tolene or dimethylformamide. It is also preferred that the group Q_1 is Cl_3CO-and that the reaction is carried out in toluene at reflux temperature.

In a preferred process variant, G and Y together are =C=O in which case the reaction takes place in an inert solvent, such as ether, at 0-100°C, preferably ambient temperature.

When L is OH or a reactive derivative thereof, the reactive derivative is often a salt, such as the lithium, sodium or potassium salt.

When the compound of formula (V) is (V)' , the reaction takes place under similar conditions as described above for Q_1 is halide.

When G is hydrogen, J-Z^1 may be a compound of formula (VII) or (VIII) when L is NH; or of formula - (IX) when L is O:

$$O=C=N-Z^1 \qquad (VII)$$

$$Q_2-\overset{\overset{O}{\|}}{C}-NH-Z^1 \qquad (VIII)$$

$$Q_3-\overset{\overset{O}{\|}}{C}-O-Z^1 \qquad (IX)$$

wherein

Z^1 is as hereinbefore defined, and Q_2 and Q_3 are leaving groups, preferably Cl_3CO.

When J-Z^1 is of formula (VII), the reaction is preferably carried out in an inert solvent, under conventional conditions 0-100°C.

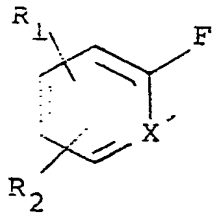
Q_2 is a leaving group as defined for Q_1 hereinafter; and the reaction is carried out in accordance with the conditions described herein for the reaction wherein G is COQ_1.

Examples of Q_3, displaceable by a nucleophile, include halogen, such as chloro and bromo; and activated hydrocarbyloxy, such as Cl_5C_6O-and Cl_3CO.

If a group Q_3 is a halide, the reaction is carried out as described above for Q_1 halide.

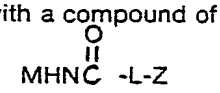
If Q_3 is activated hydrocarbyloxy, the reaction is carried out as described for Q_1 activated hydrocarbyloxy.

The invention provides a further process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (X):



(X)

with a compound of formula (XI):



(XI)

wherein M is a metal ion and the remaining variables are as hereinbefore defined; and thereafter optionally converting Z', when other than Z, to Z; converting X' when N to N^+-O^- or X to other X; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of M include alkali metals such as sodium and potassium.

The reaction may be carried out at ambient temperature or below in an inert solvent such as tetrahydrofuran or dimethylsulphoxide.

It will be apparent that compounds of the formula (I) containing an R_1 or R_2 group which is convertible to another R_1 or R_2 group are useful novel intermediates. A number of such conversions is possible not only for the end compounds of formula (I), but also for their intermediates as follows:

(i) a hydrogen substituent is convertible to a nitro substituent by nitration;

(ii) a nitro substituent is convertible to an amino substituent by reduction;

(iii) a C_{1-7} acylamino substituent is convertible to an amino substituent by deacylation;

(iv) an amino substituent is convertible to a C_{1-4} acylamino substituent by acylation with a carboxylic acid derivative;

(v) a hydrogen substituent is convertible to a halogen substituent by halogenation;

(vi) a C_{1-6} alkylthio or C_{1-6} alkylsulphinyl substituent is convertible to a C_{1-6}alkylsulphinyl or a C_{1-6} alkylsulphonyl substituent respectively by oxidation;

(vii) an amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-N-C_{1-4}alkylamino substituent is convertible to a corresponding substituent substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8}cycloalkyl, C_{1-4} alkyl or phenyl C_{1-4} alkyl groups any of which phenyl groups may be substituted by one or more groups selected from halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6}alkoxy and nitro, or disubstituted by C_{4-5}polymethylene, by N-alkylation;

(viii) an amino substituent is convertible to a C_{1-6}alkylsulphonylamino group or an aminosulphonylamino group optionally N-substituted as defined by acylation with a C_{1-6} alkylsulphonyl chloride or di-substituted aminosulphonyl chloride.

(ix) A C_{1-4} alkylamino substituent group is convertible to a N-(C_{1-6} alkylsulphonyl)N-C_{1-4}alkylamino group or an N-(amino sulphonyl)N-C_{1-4}alkylamino group optionally N-substituted as defined by acylation with a C_{1-6} alkylsulphonyl chloride or di-substituted aminosulphonyl chloride.

Conversions (i) to (ix) are only exemplary and are not exhaustive of the possibilities.

In regard to (i), nitration is carried out in accordance with known procedures.

In regard to (ii), the reduction is carried out with a reagent suitable for reducing nitroanisole to aminoanisole.

In regard to (iii), deacylation is carried out by treatment with a base, such as an alkali metal hydroxide.

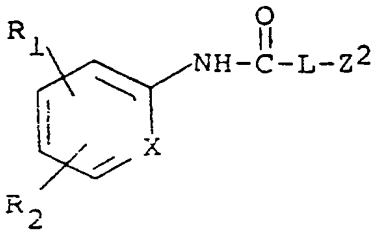
In regard to (iv), (viii), and (ix) the acylation is carried out with an acylating agent, such as the corresponding acid or acid chloride. Formylation is carried out with the free acid.

In regard to (v), halogenation is carried out with conventional halogenating agents.

In regard to (vi), oxidation is carried out at below ambient temperatures in a non-aqueous solvent, such as a chlorinated hydrocarbon, in the presence of an organic peracid, such as 3-chloroperbenzoic acid, or in water in the presence of a soluble strong inorganic oxidant, such as an alkali metal permanganate or in aqueous hydrogen peroxide. It will be realised that this process may also N-oxidise the N-moiety of a side chain (a), (b) or (c) and suitable precautions will routinely be taken by those skilled in the art.

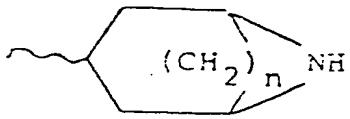
In regard to (vii), alkylation is carried out with a corresponding alkylating agent such as the chloride or bromide under conventional conditions.

Z' when other than Z may have a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups as defined for R_1 and R_2. Such benzyl groups may, for example, be removed, when R_1 or R_2 is not halogen, by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (XII):

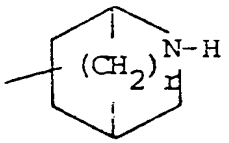


(XII)

wherein Z_2 is of formula (d) or (e)



(d)



(e)

wherein the variables are as defined in formula (I).

This invention also provides a further process for the preparation of a compound of the formula (I) which comprises N-alkylating a compound of formula (XII), and optionally forming a pharmaceutically acceptable salt, of the resulting compound of the formula (I).

In this further process of the invention 'N-alkylation' comprises the substitution of the N-atom depicted in formula (XII) by any group R_3/R_4 as hereinbefore defined. This may be achieved by reaction of the compound of formula (XII) with a compound R_3Q_4 or R_4Q_4 wherein R_3 and R_4 are as hereinbefore defined and Q_4 is a leaving group.

Suitable values for Q_4 include groups displaced by nucleophiles such as Cl, Br, I, OSO_2CH_3 or $OSO_2C_6H_4pCH_3$.

Favoured values for Q_4 include Cl, Br and I.

The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slight above.

Alternatively, 'N-alkylation' may be effected under conventional reductive alkylation conditions when the group R_3 or R_4 in the compound of formula (I) contains a methylene group adjacent to the N-atom in the bicycle.

Interconverting R_3 or R_4 in the compound of the formula (XII) before coupling with the compound of the formula (V) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C_{2-7} alkanoyl group, before R_3/R_4 interconversion.

When R_3 or R_4 in the compound of formula (VI) contains a methylene group adjacent to the N-atom in the bicycle it is often convenient in the preparation of such a compound of formula (VI) to prepare the corresponding compound wherein the methylene group is replaced by -CO-, or for R_3 or R_4 is methyl, where the methyl group is replaced by esterified carboxyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (VI).

Compounds of formula (I) wherein X' is N may be converted to compounds of formula (I) wherein X is N^+-O^- by conventional oxidation, using, for example, hydrogen peroxide or m -chloroperbenzoic acid.

Compounds of formula (I) wherein R_6 is CO_2H may be converted to compounds of formula (I) wherein R_6 is CO_2R_7' wherein R_7' is C_{1-6} alkyl, or R_6 is $CONR_8R_9$ by conventional esterification or amination respectively.

The compounds of formula (V) and (VI) are known or are preparable analogously to, or routinely from, known compounds.

Compounds of the formula (VI) wherein Z is of formula (c) may be prepared as described in European Patent Publication No. 115933 or by analogous methods thereto.

Compounds of the formula (XII) are novel and form an aspect of the invention.

It will be realised that in the compound of the formula (I) the -CO-L-linkage may have an endo or exo orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the endo and exo isomer may if desired be synthesised from the corresponding endo or exo form of the compound of the formula (VI).

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally. The acid addition salts may be formed, for example, by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT antagonists and it is thus believed may generally be used in the treatment or prophylaxis of migraine, cluster headaches and trigeminal neuralgia. Compounds which are 5-HT antagonists may also be of potential use in the treatment of CNS disorders such as anxiety and psychosis; arrhythmia, obesity and irritable bowel syndrome.

The compounds of the present invention also have anti-emetic activity; in particular that of preventing cytotoxic agent or radiation induced nausea and vomiting. Examples of cytotoxic agents include cisplatin, doxorubicin and cyclophosphamide.

The compounds of the present invention also have gastric motility enhancing activity, useful in the treatment of disorders such as retarded gastric emptying, dyspepsia, flatulence, oesophagal reflux and peptic ulcer.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of migraine, cluster headache, trigeminal neuralgia and/or emesis in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

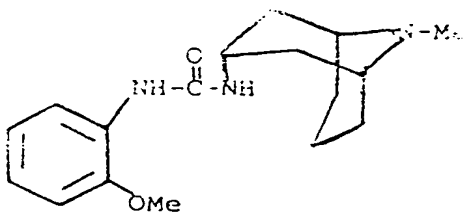
The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

The following Examples illustrate the preparation of compounds of formula (I).

N.B. Nomenclature is based on Chemical Abstracts Index Guide 1977 published by the American Chemical Society.

Example 1

(endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-N'-2-methoxyphenyl urea (E1)

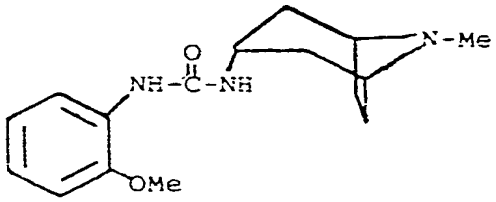


(E1)

To a stirred solution of (endo)-9-methyl-9-azabicyclo [3.3.1]-nonan-3-amine (1.6g) in Et_2O (50ml) at 0°C was added dropwise a solution of 2-methoxyphenyl isocyanate (1.5g) in Et_2O (5 ml). The reaction mixture was then stirred at room temperature overnight and the title compound (E1) collected by filtration and dried - (2.5g 80%).
m.p. 203-4°C Prepared similarly was:

Example 2

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-, 2-methoxyphenyl urea (E2)

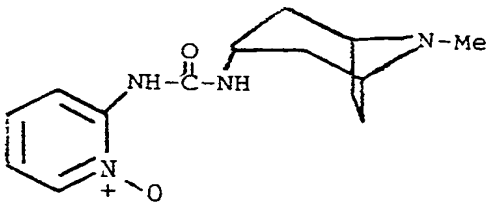


(E2)

m.p. 210-11°
^{1}H-NMR ($CDCl_3$, 79.5MHz)
δ 8.00 -7.75 (m, 1H)
7.20 -6.70 (m, 4H)
5.25 (d, 1H)
4.20 -3.75 (m, 4H including 3.85, s, 3H)
3.20 -2.95 (m, 2H)
2.50 -1.50 (m, 1H)

Example 3

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-pyridyl-1-oxide)urea (E3)



(E3)

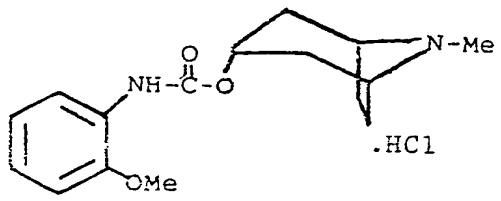
A solution of (endo)-8-methyl-8-azabicyclo[3,2,1]-octan-3-amine (0.7g) and pyridino[1',2'-2,3]-1-oxa-2,4-diazol-5-one (0.65g) in xylene (25ml) was heated under reflux under N_2 for 18h. The reaction mixture was allowed to cool, concentrated in vacuo and the residue purified by column chromatography on alumina to give the title compound (0.6g) m.p. 229-31° (dec)
^{1}H NMR ($CDCl_3$, 270 MHz)
δ 10.04 (s, 1H)
8.48 (dm, 1H)
8.11 (dm, 1H)
7.48 (brd, 1H)
7.37 (tm, 1H)

6.87 (tm, IH)
4.00 (q, IH)
3.I3 (brs, 2H)
2.35-2.20 (m, 5H including 2.28, s, 3H)
2.05-I.75 (m, 6H)

Example 4 to 27.

The following examples were prepared by a procedure analogous to that used for Example I.

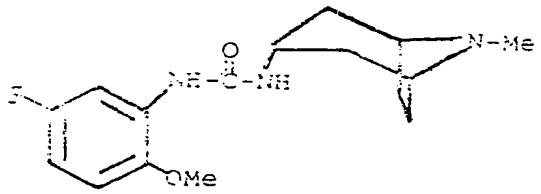
(endo)-O-(8-Methyl-8-azabicyclo[3,2,I]oct-3-yl)-N-(2-methoxyphenyl)carbamate monohydrochloride (E4)



(E4)

m.p. 240-2°
'H NMR ($CDCl_3$, 270 MHz)
δ 8.00 (brd, IH)
7.I5-6.85 (m, 4H)
5.I4 (t, IH)
3.88 (s, 3H)
3.78 (brd, 2H)
3.20-2.00 (m, IIH including 2.78, s, 3H)

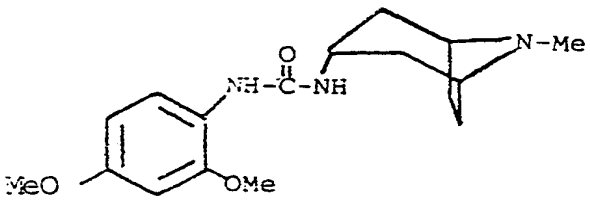
(endo)-N-(8-Methyl-8-azabicyclo[3,2,I]oct-3-yl)-N'-(5-fluoro-2-methoxyphenyl)urea (E5)



(E5)

m.p. I89-94°
'H NMR ($CDCl_3$ + CD_3OD)
δ 7.95 (dd, IH)
6.77 (dd, IH)
6.58 (dt, IH)
3.99-3.80 (m, 4H including 3.86, s, 3H)
3.20 (brs. 2H)
2.33 (s, 3H)
2.30-I.95 (m, 8H)
I.77 (brd, 2H)

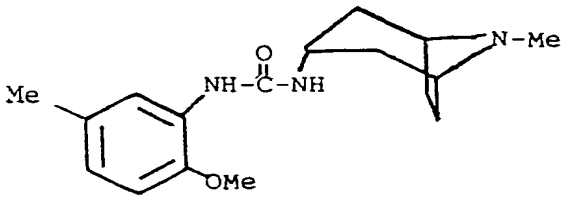
(endo)-N-(8-Methyl-8-azabicyclo[3,2,I]oct-3-yl)-N-(2,4-dimethoxyphenyl)urea (E6)



(E6)

m.p. 170-1°
^{1}H NMR ($CDCl_3$ 400 MHz)
δ 7.58 (d, 1H)
6.40-4.40 (m, 3H including 6.49, s, 1H)
5.24 (brd, 1H)
3.96 (q, 1H)
3.80 (s, 6H)
3.12 (brs, 2H)
2.27 (s, 3H)
2.25-2.15 (m, 2H)
2.08-1.98 (m, 2H)
1.72-1.62 (m, 3H)

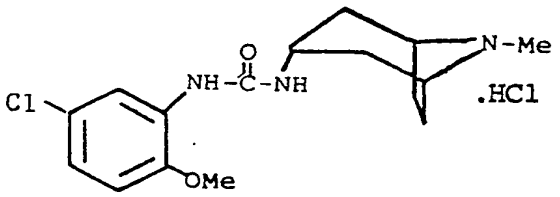
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-methoxy-5-methylphenyl)urea (E7)



(E7)

m.p. 190-1°
^{1}H NMR ($CDCl_3$, 270 MHz)
δ 7.73 (brs, 1H)
6.85-6.70 (m, 3H)
5.31 (brd, 1H)
3.98 (q, 1H)
3.80 (s, 3H)
3.13 (brs, 2H)
2.35-2.00 (m, 10H including 2.29, s, 3H and 2.26 s, 3H)
1.85-1.64 (m, 4H)

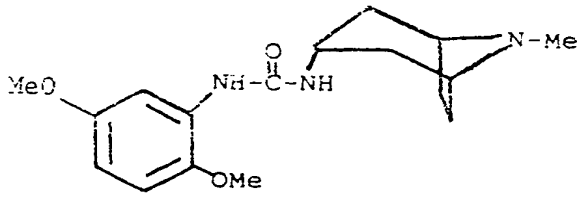
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(5-chloro-2-methoxyphenyl)urea monohydrochloride (E8)



(E8)

m.p. 259-63°
^{1}H NMR (d^6-DMSO, 400 MHz)
δ 10.90 (brs, 1H)
8.30-8.20 (m, 2H)
7.28 (d, 1H)
6.85-6.80 (m, 2H)
3.96 (q, 1H)
3.89 (s, 3H)
3.85-3.70 (m, 2H)
2.80-2.65 (m, 5H)
2.55-2.45 (m, 2H)
2.30-2.20 (m, 2H)
2.09 (brd, 2H)

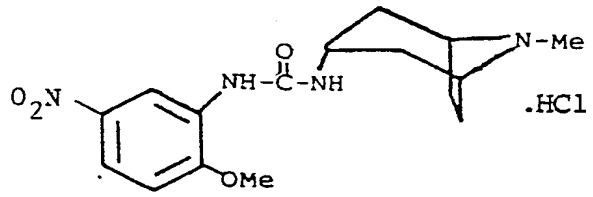
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2,5-dimethoxyphenyl)urea (E9)



(E9)

m.p. 192°
^{1}H NMR ($CDCl_3$, 270 MHz)
δ 7.72 (d, 1H)
6.98 (brd, 1H)
6.78 (d, 1H)
6.51 (dd, 1H)
5.36 (brm, 1H)
4.00 (q, 1H)
3.80 (s, 3H)
3.76 (s, 3H)
3.16 (brs, 2H)
2.35-2.20 (m, 5H including 2.30, s, 3H)
2.15-2.05 (m, 2H)
1.98-1.67 (m, 4H)

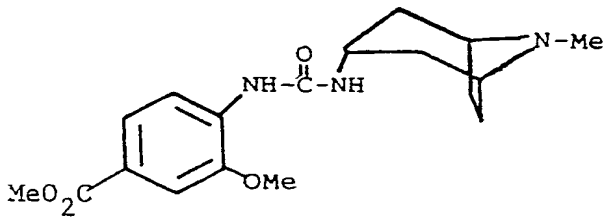
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-methoxy-5-nitrophenyl)urea monohydrochloride (E10)



(E10)

m.p. 237-250°
^{1}H NMR ($CDCl_3$/d^6-DMSO; 400 MHz)
δ 10.40 (brs, 1H)
9.12 (d, 1H)
8.51 (s, 1H)
7.83 (dd, 1H)
7.41 (d, 1H)
7.07 (d, 1H)
4.04 (s, 3H)
3.94 (q, 1H)
3.85 (brs, 2H)
2.72 (d, 3H)
2.66-2.52 (m, 2H)
2.48-2.16 (m, 4H)
2.08 (d, 2H)

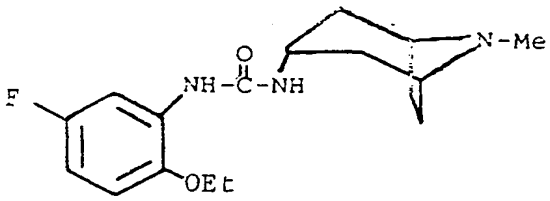
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-methoxy-4-methoxycarbonylphenyl)urea (E11)



(E11)

m.p. 108-112°
^{1}H NMR ($CDCl_3$, 400Hz)
δ 8.24 (d, 1H)
7.64 (dd, 1H)
7.50-7.44 (m, 2H)
5.76 (brd, 1H)
4.02 (q, 1H)
3.90 (s, 3H)
3.83 (s, 3H)
3.15 (brs, 2H)
2.34-2.20 (m, 5H including 2.30, s, 3H)
2.14-2.00 (m, 2H)
1.92-1.80 (m, 2H)
1.72 (d, 2H)

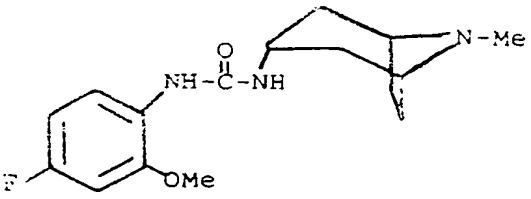
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-ethoxy-5-fluorophenyl)urea (E12)



(E12)

m.p. 185-8°
^{1}H NMR (CD_3OD, 79.5 MHz)
δ 7.92 (dd, 1H)
6.92 (dd, 1H)
6.61 (dt, 1H)
4.30-3.75 (m, 3H)
3.20 (brs, 2H)
2.50-1.25 (m, 14H including 2.34, s, 3H and 1.46, t, 3H)

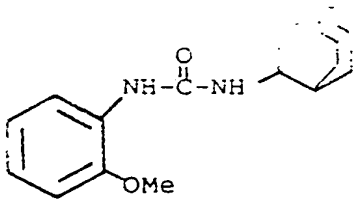
(endo)-N-(8-Methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(4-fluoro-2-methoxyphenyl)urea (E13)



(E13)

m.p. 191-4°
^{1}H NMR (CD_3OD 270 MHz)
δ 7.89 (dd, 1H)
6.75 (dd, 1H)
6.57 (dt, 1H)
4.00-3.80 (m, 4H including 3.87, s, 3H)
3.22-3.05 (m, 2H)
2.32-1.65 (m, 13H including 2.27, s, 3H)

N-(1-Azabicyclo[2,2,2]oct-3-yl)-N'-(2-methoxyphenyl) urea (E14)

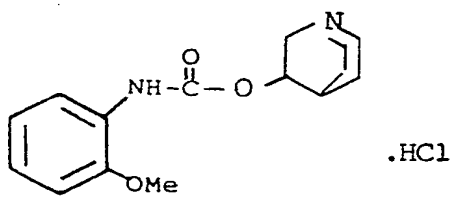


(E14)

m.p. 197-8°
^{1}H NMR ($CDCl_3$, 270 MHz)
8.15-8.00 (m, 1H)
7.06-6.80 (m, 4H)

5.28 (brd, IH)
3.96-3.80 (m, 4H including 3.83, s, 3H)
3.36 (m, IH)
2.95-2.70 (m, 4H)
2.53 (dd, IH)
1.98 (brs, IH)
1.80-1.60 (m, 3H)
1.55-1.40 (m, IH)

O-(1-Azabicyclo[2.2.2]oct-3-yl)-N-(2-methoxyphenyl) carbamate monohydrochloride (E15)

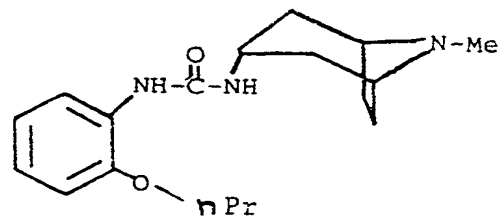


.HCl

(E15)

m.p. 227-9°
^{1}H NMR (d^6-DMSO, 270 MHz)
δ 10.50 (brs, IH)
8.62 (s, IH)
7.67 (d, IH)
7.12-7.00 (m, 2H)
6.98-6.86 (m, IH)
5.00-4.90 (m, IH)
3.82 (s, IH)
3.65 (dd, IH)
3.40-3.00 (m, 7H)
2.28 (brs, IH)
2.15-1.65 (m, 4H)

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-n-propyloxyphenyl)urea (E16)

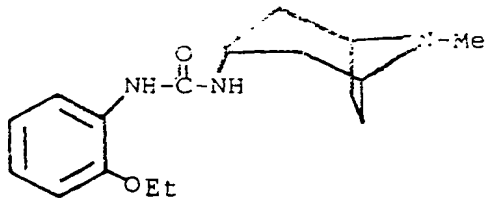


(E16)

m.p. 163-5°
^{1}H NMR ($CDCl_3$, 270 MHz)
δ 7.85 (dd, IH)
7.05-6.84 (m, 3H)
6.77 (brs, IH)
5.23 (brd, IH)
4.00-3.88 (m, 3H including 3.97, t, 2H)
3.17 (brs, 2H)
2.35-2.20 (m, 5H including 2.30, s, 3H)

2.12-2.02 (m, 2H)
1.90-1.66 (m, 6H)
1.02 (t, 3H)

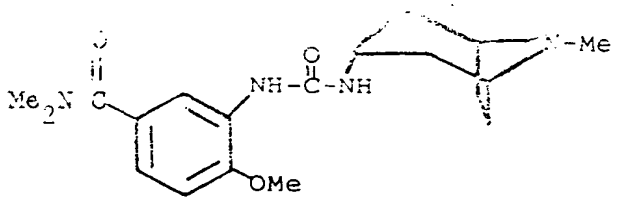
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-ethoxyphenyl)urea (E17)



(E17)

m.p. 170-5°
^{1}H NMR ($CDCl_3$, 400 MHz)
δ 7.90 (dd, 1H)
7.04-6.82 (m, 4H)
5.52 (brd, 1H)
4.07 (q, 2H)
3.95 (q, 1H)
3.15 (brs, 2H)
2.35-2.20 (m, 5H including 2.30, s, 3H)
2.10-2.00 (m, 2H)
1.85-1.68 (m, 4H)
1.42 (t, 3H)

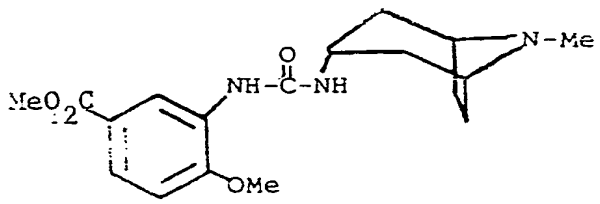
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(5-dimethylaminocarbonyl-2-methoxyphenyl)urea (E18)



(E18)

^{1}H NMR ($CDCl_3$, 270 MHz)
δ 8.09 (d, 1H)
7.21 (brs, 1H)
7.03 (dd, 1H)
6.87 (d, 1H)
5.84 (brd, 1H)
3.93 (q, 1H)
3.80 (s, 3H)
3.15 (brs, 2H)
3.06 (s, 6H)
2.32 (s, 3H)
2.32-2.16 (m, 2H)
2.15-1.87 (m, 4H)
1.71 (brd, 2H)

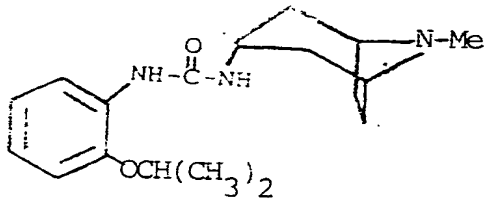
(endo)-N-(8-Methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(5-methoxycarbonyl-2-methoxyphenyl)urea (E19)



(E19)

m.p. 125-6°
^{1}H NMR ($CDCl_3$, 270 MHz)
δ 8.64 (d, 1H)
7.73 (dd, 1H)
7.01 (brs, 1H)
6.86 (d, 1H)
5.53 (brd, 1H)
4.00 (q, 1H)
3.97 (s, 3H)
3.95 (s, 3H)
3.18 (brs, 2H)
2.35-2.20 (m, 5H including 2.31, s, 3H)
2.18-2.05 (m, 2H)
1.92-1.79 (m, 4H)

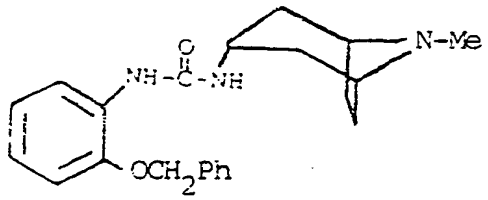
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-isopropoxyphenyl)urea (E20)



(E20)

m.p. 163-4°
^{1}H-NMR ($CDCl_3$, 270MHz)
δ 7.87 (dd, 1H)
7.01-6.86 (m, 3H)
6.78 (brs, 1H)
5.20 (brd, 1H)
4.56 (m, 1H)
3.94 (m, 1H)
3.17 (brs, 2H)
2.30 (s, 3H)
2.27-2.20 (m, 2H)
2.10-2.03 (m, 2H)
1.80-1.68 (m, 4H)
1.35 (d, 6H)

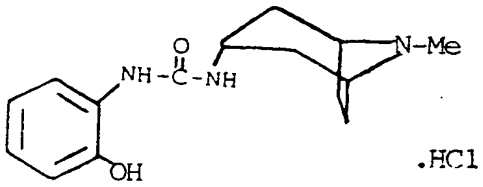
(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-benzyloxyphenyl)urea (E21)



(E21)

m.p. 174-6°
^{1}H-NMR ($CDCl_3$, 270MHz)
δ 7.91 (dd, 1H)
7.43-7.32 (m, 5H)
7.00-6.90 (m, 3H)
7.78 (brs, 1H)
5.13 (brd, 1H)
5.06 (s, 2H)
3.88 (m, 1H)
3.11 (brs, 2H)
2.27 (s, 3H)
2.23-2.12 (m, 2H)
2.08-2.00 (m, 2H)
1.78-1.60 (m, 4H)

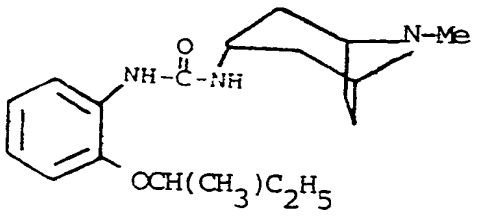
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-hydroxyphenyl)urea hydrochloride (E22)



(E22)

m.p. 267-8°
^{1}H-NMR (d^6-DMSO, 270MHz)
δ 10.33 (brs, 1H)
9.96 (s, 1H)
8.28 (s, 1H)
7.88 (dd, 1H)
7.18 (d, 1H)
6.84-6.63 (m, 3H)
3.80 (brm, 3H)
2.65 (s, 3H)
2.50-2.37 (m, 2H)
2.30-2.15 (m, 4H)
1.96-1.82 (m, 2H)

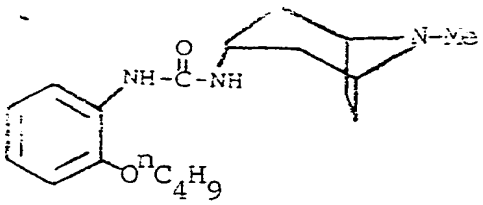
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-sec-butyloxyphenyl)urea (E23)



(E23)

m.p. 136-7°
^{1}H-NMR ($CDCl_3$, 270MHz)
δ 7.87 (dd, 1H)
7.00-6.78 (m, 4H)
5.20 (brd, 1H)
4.33 (m, 1H)
3.93 (m, 1H)
3.14 (brs, 2H)
2.31-2.17 (m, 5H including 2.28, s, 3H)
2.10-2.01 (m, 2H)
1.80-1.57 (m, 6H)
1.28 (d, 3H)
0.98 (t, 3H)

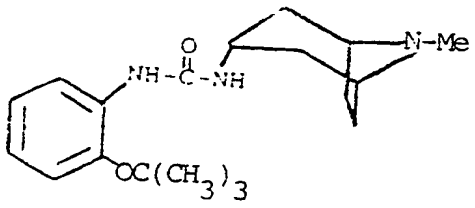
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-n-butyloxyphenyl)urea (E24)



(E24)

m.p. 139-141°
^{1}H-NMR ($CDCl_3$, 270MHz)
δ 7.86 (dd, 1H)
7.02-6.83 (m, 3H)
6.76 (s, 1H)
5.19 (brd, 1H)
4.00 (t, 2H)
3.93 (m, 1H)
3.15 (brs, 2H)
2.28 (s, 3H)
2.25-2.17 (m, 2H)
2.11-2.03 (m, 2H)
1.81-1.65 (m, 6H)
1.47 (m, 2H)
0.98 (t, 3H)

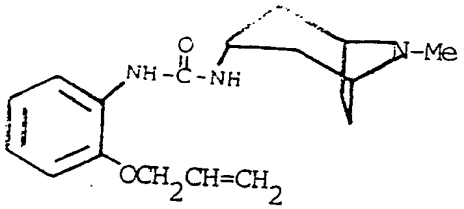
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-tert-butyloxyphenyl)urea (E25)



(E25)

m.p. 150-1°
^{1}H-NMR ($CDCl_3$, 270MHz)
δ 7.80 (dd, 1H)
7.07-6.86 (m, 4H)
5.38 (brd, 1H)
3.93 (m, 1H)
3.16 (brs, 2H)
2.31-2.17 (m, 5H including 2.29, s, 3H)
2.10-2.01 (m, 2H)
1.80-1.67 (m, 4H)
1.39 (s, 9H)

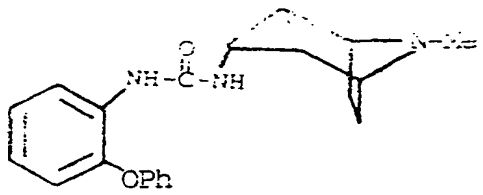
(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-allyloxyphenyl)urea (E26)



(E26)

m.p. 156-7°
^{1}H-NMR ($CDCl_3$, 270MHz)
δ 7.89 (dd, 1H)
7.00-6.82 (m, 3H)
6.78 (s, 1H)
6.12-5.97 (m, 1H)
5.42-5.26 (m, 2H)
5.20 (brd, 1H)
4.58 (m, 2H)
3.96 (m, 1H)
3.16 (brs, 2H)
2.32-2.17 (m, 5H including 2.30, s, 3H)
2.12-2.03 (m, 2H)
1.78-1.66 (m, 4H)

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-phenoxyphenyl)urea (E27)

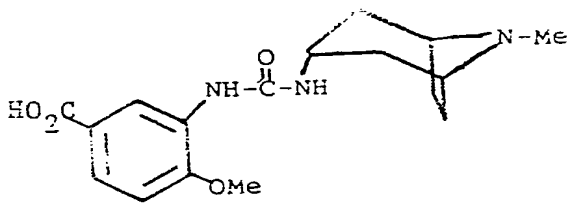


(E27

m.p. 198-9°
^{1}H-NMR ($CDCl_3$, 270MHz)
δ 8.06 (dd, 1H)
7.36-7.26 (m, 2H)
7.15-7.05 (m, 2H)
6.99-6.82 (m, 5H)
5.22 (brd, 1H)
3.90 (m, 1H)
3.11 (brs, 2H)
2.27 (s, 3H)
2.25-2.13 (m, 2H)
2.07-1.99 (m, 2H)
1.74-1.56 (m, 4H)

Example 28

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(5-hydroxycarbonyl-2-methoxyphenyl)urea (E28)

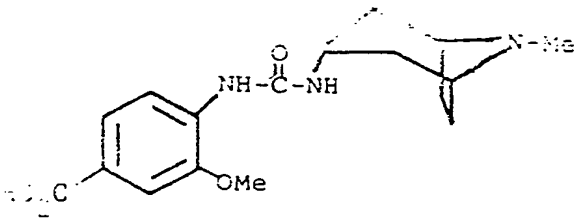


(E28)

The methyl ester (Example 19, 1.0g) was heated under reflux in a methanol (10ml) and aqueous (10ml) solution of 2.5N NaOH (5ml) for four hours. The methanol was removed in vacuo and the aqueous residue acidified to pH 7.0. The crystalline product was collected and dried (0.86g). m.p. 232-5°
^{1}H NMR (CD_3OD/DCl, 270 MHz)
δ 8.70 (d, 1H)
7.67 (dd, 1H)
7.03 (d, 1H)
4.02-3.85 (m, 6H including 3.96, s, 3H)
2.80 (s, 3H)
2.56-2.35 (m, 6H)
2.17 (brd, 2H)

Example 29

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-N'-(4-hydroxycarbonyl-2-methoxyphenyl)urea (E29)

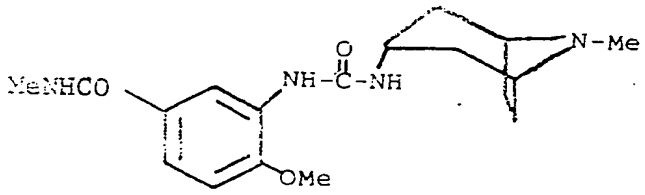


(E29

Following the procedure outlined in Example 28, Example II was converted to the title compound. m.p. 213-20°
'H-NMR (CD_3OD/DCl, 270 MHz)
δ 8.14 (d, IH)
7.57 (dd, IH)
7.53 (d, IH)
4.00-3.85 (m, 6H including 3.93, s, 3H)
2.80 (s, 3H)
2.60-2.30 (m, 6H)
2.16 (brd, 2H)

Example 30

(endo)-N-(8-Methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(5-methylaminocarbonyl-2-methoxyphenyl)urea (E30)



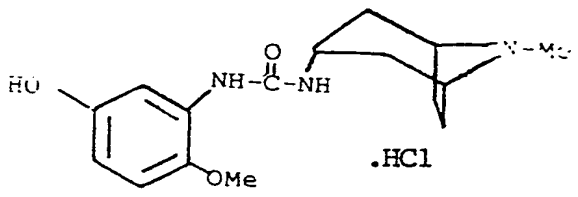
(E30

A solution of Example 28 (0.5g) in thionyl chloride (2ml) was stirred at room temperature for Ih. the thionyl chloride was rmeoved in vacuo and the residue treated with a solution of methylamine (4 equivalents) in CH_2Cl_2 (25ml). The reaction was stirred overnight, washed with aqueous $NaHCO_3$ solution, dried and concentrated. The residue was crystallised from ethyl acetate to give the title compound. 'H NMR (d^6-DMSO, 270 MHz)
δ 8.55 (d, IH)
8.23-8.10 (m, 2H)
7.37 (dd, 2H)
7.00 (d, IH)
6.91 (brd, IH)
3.90 (s, 3H)
3.77 (q, IH)
3.23 (brs, 2H)
2.73 (d, 3H)
2.31 (s, 3H)

2.20-1.90 (m, 6H)
1.65 (brd, 2H)

Example 31

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(5-hydroxy-2-methoxyphenyl)urea monohydrochloride (E31)



(E31)

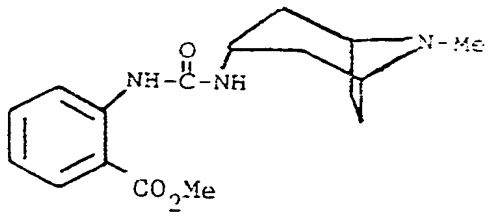
The 5-benzyloxy-2-methoxyphenyl isocyanate and (endo)-8-methyl-8-azabicyclo[3,2,1]octan-3-amine was converted via the procedure outlined in Example 1 to (endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(5-benzyloxy-2-methoxyphenyl)urea which was converted to the monohydrochloride salt.

The hydrochloride salt was hydrogenated at atmospheric pressure and room temperature over 10% Pd/C in ethanol to give the title compound. ^{1}H NMR (d_6-DMSO, 270 MHz)

δ 8.81 (s, 1H)
8.10 (s, 1H)
7.68 (d, 1H)
7.16 (d, 1H)
6.75 (d, 1H)
6.24 (dd 1H)
4.20-4.05 (m, 1H)
3.85-3.70 (m, 5H)
3.17 (d, 3H)
2.65 (s, 2H)
2.55-2.15 (m, 4H)
1.90 (brd, 2H)

Example 32

(Endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-methoxycarbonylphenyl)urea (E32)



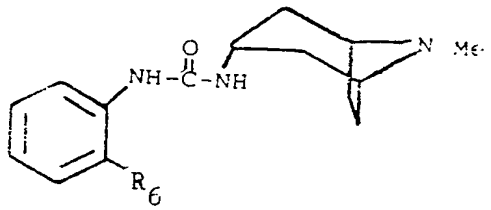
(E32)

A solution of phosgene in toluene (12.5%, 7.5ml) was added to a stirred solution of methyl anthranilate - (1.2g) in dry CH_2Cl_2 (100ml) at 0°C. After 10 min, triethylamine (2.5ml) was added. After a further 10 min, a solution of (endo)-8-methyl-8-azabicyclo[3.2.1]-octan-3-amine (1.12g) in CH_2Cl_2 (10ml) was added and the reaction stirred to room temperature for 4h. The reaction mixture was then washed with excess sat. $NaHCO_3$

solution, dried (K_2CO_3) and concentrated in vacuo. Recrystallisation of the residue from ethyl acetate/petrol gave the title compound (E32) (1.8g) m.p. 125-7°
^{1}H NMR (δ, $CDCl_3$
10.28 (brs, 1H)
8.50 (dm, 1H)
7.96 (dm, 1H)
7.48 (tm, 1H)
6.95 (tm, 1H)
5.01 (brd, 1H)
4.00 (q, 1H)
3.90 (s, 3H)
3.17 (brs, 2H)
2.40-2.05 (m, 7H including 2.30, s, 3H)
1.95-1.70 (m, 4H)

Examples 33 to 38

The following examples were prepared by a similar procedure to that described in Example 32.



Compound	R_6	m.p. °C
33	CO_2Et	145-7
34	$CONMe_2$	196-7
35	SO_2NMe_2	162-3
36	NO_2	177-8
37	CH_2OCH_3	148-9
38	SMe	284-5*

* hydrochloride salt.

Pharmacology

Antagonism of the von Bezold-Jarisch reflex

The compounds were evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

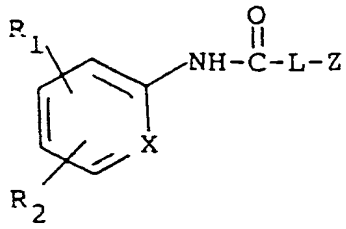
Male rats 250-350g, were anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) was given repeatedly by the intravenous route and changes in heart rate quantified. Compounds were given intravenously and the concentraton required to reduce the 5-HT-evoked response to 50% of the control response (ED_{50}) was then determined.

The compound of Example 2 gave an ED_{50} value of 2µg/kg i.v.

The compounds of Examples 14, 15, 24, 26, and 27 were active at doses of 2, 3.4, 2.2, 22.5 and 1.8 µg/kg i.v. respectively.

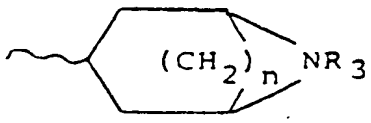
Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

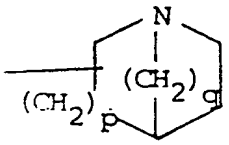


(I)

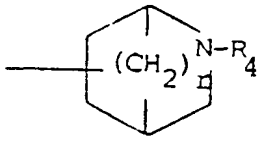
wherein
L is NH or O;
X is a moiety capable of hydrogen bonding to the NH group depicted in formula (I);
R_1 and R_2 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6}alkylsulphinyl, carboxy, C_{1-6} alkoxycarbonyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4}alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8}cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5}polymethylene; and
Z is a group of formula (a), (b) or (c)



(a)



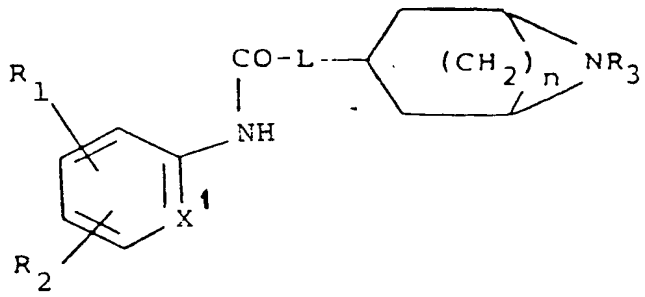
(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and
R_3 or R_4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8}cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl.

2. A compound according to claim 1 or formula (II):



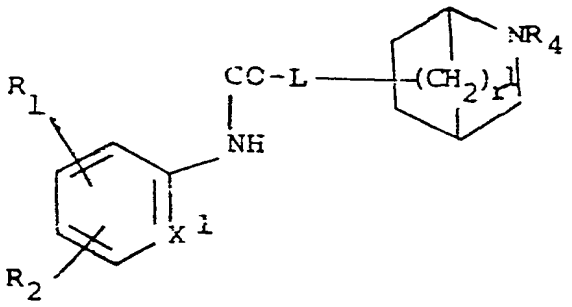
(II)

wherein X' is COR_5 or a group C-R_6 as defined in claim 1; and the remaining variables are as defined in claim 1.

3. A compound according to claim 2 wherein n is 2.

4. A compound according to claim 2 or 3 wherein R_3 is methyl or ethyl.

5. A compound according to claim 1 of formula (IV):



(IV)

wherein r' is 1 or 2 and the remaining variables are as defined in claims 1 and 2.

6. A compound according to claim 5 wherein r is 2.

7. A compound according to any one of claims 1 to 6 wherein L is NH.

8. A compound according to any one of claims 1 to 7 wherein R_1 and R_2 are both hydrogen.

9. A compound according to any one of claims 1 to 8 wherein X is C-OCH_3, C-OC_2H_5, C-OC_3H_7, C-CO_2CH_3, C-$CO_2C_2H_5$ or $SO_2N(CH_3)_2$.

10. (endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-N'-2-methoxyphenyl urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-2-methoxyphenyl urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'(2-pyridyl-1-oxide)urea,

(endo)-O-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N-(2-methoxyphenyl)carbamate,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(5-fluoro-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N-(2,4-dimethoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2-methoxy-5-methylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(5-chloro-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2,5-dimethoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2-methoxy-5-nitrophenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2-methoxy-4-methoxycarbonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2-ethoxy-5-fluorophenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(4-fluoro-2-methoxyphenyl)urea,

N-(1-azabicyclo[2,2,2]oct-3-yl)-N'-(2-methoxyphenyl)urea,

O-(1-azabicyclo[2,2,2]oct-3-yl)-N-(2-methoxyphenyl)carbamate,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2-n-propyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2-ethoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(5-dimethylaminocarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(5-methoxycarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2-isopropoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-N'-(2-benzyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(2-hydroxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(2-sec-butyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(2-n-butyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(2-tert-butyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(2-allyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(2-phenoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(5-hydroxycarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl]-N'-(4-hydroxycarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(5-methylaminocarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N'-(5-hydroxy-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N'-(2-methoxycarbonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N'-(2-ethoxycarbonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N'-(2-dimethylaminocarbonylphenyl)urea,

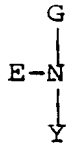
(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N'-(2-dimethylaminosulphonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N'-(2-nitrophenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N'-(2-methoxymethylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N'-(2-methylthiophenyl)urea, or a hydrochloride salt of any of the foregoing.

II. A process for the preparation of a compound of formula (I), as defined in Claim I, or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (V):

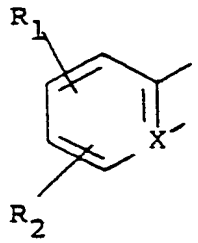


(V)

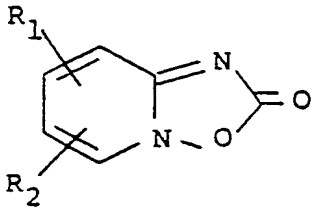
with a compound of formula (VI):

J-Z' (VI)

wherein E is:

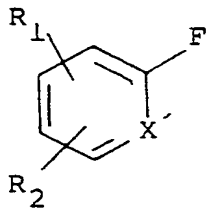


wherein X' is X as defined, or N, and Y is hydrogen or joined to G as defined, or (when X is $N^{+}-O^{-}$) E and Y together are joined to G to form (V)ᶜ:



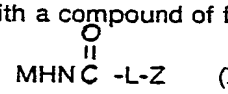
G is COQ, where Q, is a group displaceable by a nucleophile, G and Y together =C=O or G is joined to E as defined, or G is hydrogen (when Y is hydrogen); and, when G is COQ, or G-N-Y is N=C=O, J is NH_2, or OH or a reactive derivative thereof or, when G is hydrogen, J is a group containing an activated carbonyl group capable of forming a CO-L-linkage with the compound of formula (V); Z' is Z as defined or Z wherein R_3/R_4 is replaced by a hydrogenolysable protecting group; and the remaining variables are as defined in claim I; and thereafter optionally converting any R_1 and R_2 group to another R_1 and R_2 group respectively, converting Z', when other than Z, to Z; converting X' when N to $N^{+}-O^{-}$ or X to other X: and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

I2. A process for the preparation of a compound of formula (I), as defined in Claim I or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (X):



(X)

with a compound of formula (XI):



(XI)

wherein M is a metal ion and the remaining variables are as defined in claim I; and thereafter optionally converting Z',when other than Z, to Z'; converting X' when N to $N^{+}-O^{-}$ or X to other X; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

I3. A pharmaceutical composition comprising a compound according to any one of claims I to I0, and a pharmaceutically acceptable carrier.

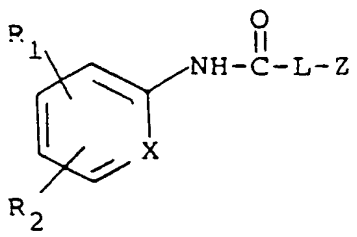
I4. A compound according to any one of claims I to I0, for use as an active therapeutic substance.

I5. A compound according to any one of claims I to I0 for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

I6. Use of a compound according to any one of claims I to I0 in the preparation of a medicament for the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

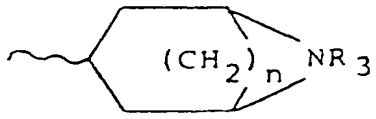
Claims for the following Contracting State :ES

1. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof:

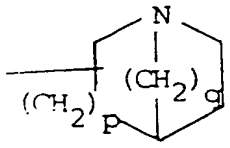


(I)

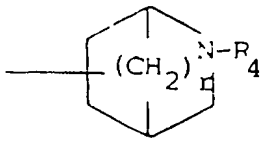
wherein
L is NH or O;
X is a moiety capable of hydrogen bonding to the NH group depicted in formula (I);
R_1 and R_2 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6}alkylsulphinyl, carboxy, C_{1-6} alkoxycarbonyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4}alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8}cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5}polymethylene; and
Z is a group of formula (a), (b) or (c)



(a)

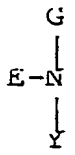


(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and
R_3 or R_4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8}cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl;
which process comprises reacting a compound of formula (V):

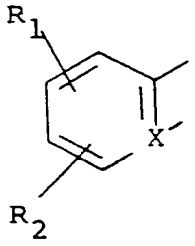


(V)

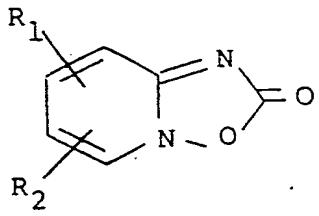
with a compound of formula (VI):

J-Z' (VI)

wherein E is:

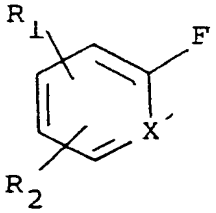


wherein X' is X as defined, or N, and Y is hydrogen or joined to G as defined, or (when X is N^+-O^-) E and Y together are joined to G to form (V)':



G is COQ' where Q' is a group displaceable by a nucleophile, G and Y together =C=O or G is joined to E as defined, or G is hydrogen (when Y is hydrogen); and, when G is COQ, or G-N-Y is N=C=O, J is NH_2, or OH or a reactive derivative thereof or, when G is hydrogen, J is a group containing an activated carbonyl group capable of forming a CO-L-linkage with the compound of formula (V); Z' is Z as defined or Z wherein R_3/R_4 is replaced by a hydrogenolysable protecting group, and thereafter optionally converting any R_1 and R_2 group to another R_1 and R_2 group respectively, converting Z', when other than Z, to Z; converting X' when N to N^+-O^- or X to other X; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

2. A process for the preparaton of a compound of formula (I), as defined in Claim I or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (X):



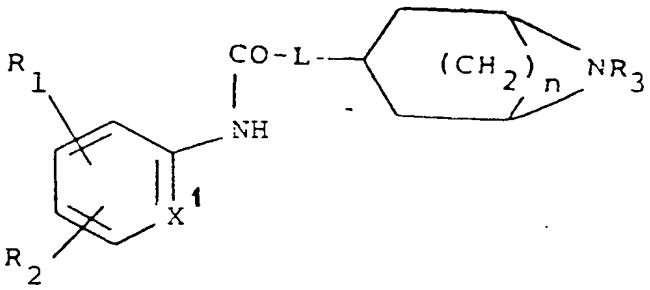
(X)

with a compound of formula (XI):

MHN-C(=O)-L-Z (XI)

wherein M is a metal ion and the remaining variables are as defined in claim I; and thereafter optionally converting Z', when other than Z, to Z; converting X' when N to N^+-O^- or X to other X: and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

2. A process according to claim I for the preparation of a compound of formula (II):



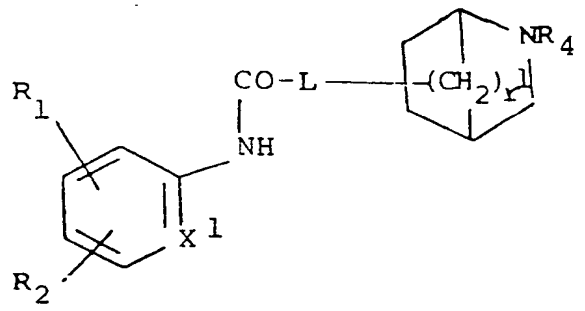
(II)

wherein X' is COR_5 or a group R_6 as defined in claim I; and the remaining variables are as defined in claim I.

3. A process according to claim 2 wherein n is 2.

4. A process according to claim 2 or 3 wherein R_3 is methyl or ethyl.

5. A process according to claim I for the preparation of a compound of formula (IV):



(IV)

wherein r' is I or 2 and the remaining variables are as defined in claims I and 2.

6. A process according to claim 5 wherein r is 2.

7. A process according to any one of claims I to 6 wherein L is NH.

8. A process according to any one of claims I to 7 wherein R_1 and R_2 are both hydrogen.

9. A process according to any one of claims I to 8 wherein X is C-OCH_3, C-OC_2H_5, C-OC_3H_7, C-CO_2CH_3, C-$CO_2C_2H_5$ or $SO_2N(CH_3)_2$

I0. A process according to claim I for the preparation of (endo)-N-(9-Methyl-9-azabicyclo-[3.3.I]non-3-yl)-N'-2-methoxyphenyl urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.I]oct-3-yl)-N'-2-methoxyphenyl urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,I]oct-3-yl)-N'-(2-pyridyl-I-oxide)urea,

(endo)-O-(8-methyl-8-azabicyclo[3,2,I]oct-3-yl)-N-(2-methoxyphenyl)carbamate,

(endo)-N-(8-methyl-8-azabicyclo[3,2,I]oct-3-yl)-N'-(5-fluoro-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,I]oct-3-yl)-N-(2,4-dimethoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,I]oct-3-yl)-N'-(2-metoxy-5-methylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,I]oct-3-yl)-N'-(5-chloro-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2,5-dimethoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-methoxy-5-nitrophenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-methoxy-4-methoxycarbonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-ethoxy-5-fluorophenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(4-fluoro-2-methoxyphenyl)urea,

N-(l-azabicyclo[2,2,2]oct-3-yl)-N′-(2-methoxyphenyl)urea,

O-(l-azabicyclo[2,2,2]oct-3-yl)-N-(2-methoxyphenyl)carbamate,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-n-propyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-ethoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(5-dimethylaminocarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′ (5-methoxycarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-isopropoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-benzyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-hydroxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-sec-butyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-n-butyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-tert-butyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-allyloxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(2-phenoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(5-hydroxycarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl]-N′-(4-hydroxycarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(5-methylaminocarbonyl-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3,2,l]oct-3-yl)-N′-(5-hydroxy-2-methoxyphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N′-(2-methoxycarbonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N′-(2-ethoxycarbonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N′-(2-dimethylaminocarbonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N′-(2-dimethylaminosulphonylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N′-(2-nitrophenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.l]oct-3-yl)-N′-(2-methoxymethylphenyl)urea,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-N'-(2-methylthiophenyl)urea, or a hydrochloride salt of any of the foregoing.

11. Use of a compound of formula (I) as defined in any one of claims 1 to 10 in the preparation of a medicament for the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

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European Patent Office
Office européen des brevets

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A3

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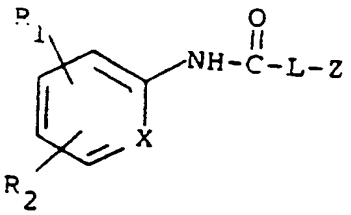
(54) **Novel compounds.**

(57) Compounds of formula (I), and pharmaceutically acceptable salts thereof:



(I)

wherein

L is NH or O;

X is a moiety capable of hydrogen bonding to the NH group depicted in formula (I);

R_1 and R_2 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulphinyl, carboxy, C_{1-6} alkoxycarbonyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4} alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-

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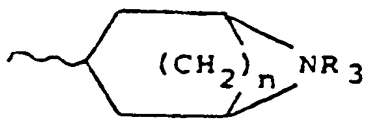
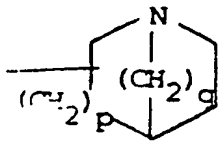
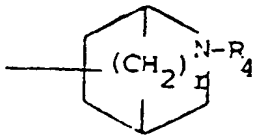
disubstituted oy C_{4-5} polymethylene; and
Z is a group of formula (a), (b) or (c)



(a)



(b)



(c)

wherein n is 2 or 3; p is I or 2; q is I to 3; r is I to 3: and
R_3 or R_4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl; having 5-HT M-receptor antagonist activity, a process for their preparation and their use as pharmaceuticals.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 87300192.9

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	US - A - 4 082 756 (BAUMAN) * Claim 1; columns 1,2; especially column 1, lines 44-46 *	1,7-9, 13,14	C 07 D 451/04 C 07 D 451/06 C 07 D 451/14 C 07 D 453/02 A 61 K 31/435 A 61 K 31/46
P,A	FR - A1 - 2 571 053 (ETAT D'ISRAEL) * Claims 1,9 *	1,8,13, 14	
A	US - A - 2 658 067 (DUSCHINSKY) * Column 1 *	1,8,9, 13,14	
A	DE - A1 - 2 645 781 (BASF AG) * Claim 2; page 8 *	1	
A	EP - A2/A3 - 0 115 933 (BEECHAM GROUP PLC) * Claims 1,10 *	1,5,9, 13-16	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	EP - A2 - 0 094 742 (BEECHAM GROUP PLC) * Claims 1,10 *	1,9,13-16	C 07 D 451/00 C 07 D 453/00 C 07 D 471/00 C 07 D 487/00
A	EP - A1 - 0 095 262 (BEECHAM GROUP PLC) * Claims 1,16 *	1,9,13-16	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	31-03-1989	PETROUSEK

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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& : member of the same patent family, corresponding document

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